PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Frants *et al.*

Serial No.: Not Yet Assigned

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Title: A gene related to migraine in man

CLEAN COPY OF CLAIMS

Mail Stop PATENT APPLICATION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following is a clean copy of the text of the claims following entry of the amendments as shown on the attached Preliminary Amendment. Replacement pages 32-36 incorporating these changes are attached hereto.

In The Claims

1. An isolated nucleic acid encoding an α1 subunit of a P/Q-type gated calcium channel or a specific fragment or homolog or derivative of said calcium channel.

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2. The nucleic acid according to claim 1, wherein said nucleic acid is a cDNA.

3. The cDNA according to claim 2, wherein said cDNA comprises a 6789 bp coding region.

4. The nucleic acid according to claim 1, wherein said cDNA is of human origin.

5. The nucleic acid according to claim 4, wherein the nucleotide sequence of said nucleic acid has at least 70% homology with the nucleotide sequence depicted in SEQ ID NO: 1-42.

6. The nucleic acid according to claim 1, wherein the nucleotide sequence of said nucleic acid has at least 90% homology with the nucleotide sequence depicted in SEQ ID NO: 1-42.

7. The nucleic acid according to claim 38, wherein said one or more mutation is at a codon in said nucleic acid which results in an amino acid change in said calcium channel respectively selected from the group consisting of codon 192: replacement of arginine by glutamine; codon 666: a replacement of threonine by methionine; codon 714, a replacement of valine by alanine; and codon 1811: a replacement of isoleucine by leucine.

8. An isolated nucleic acid according to Claim 1, wherein said nucleic acid comprises a mutation at codon 666 resulting in the replacement of threonine by methionine.

9. An isolated nucleic acid according to Claim 1, wherein said nucleic acid comprises a mutation at codon 714 resulting in the replacement of valine by alanine.

10. An isolated nucleic acid according to Claim 1, wherein said nucleic acid comprises a mutation at codon 1811 resulting in the replacement of isoleucine by leucine.

11. The isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a CA-

repeat sequence.

12. The isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a (CAG)n repeat sequence as shown in table 2.

13. The isolated nucleic acid according to claim 1, wherein the coding sequence of said nucleic acid comprises a polymorphism.

14. The isolated nucleic acid according to claim 13, wherein said polymorphism comprises a nucleotide change shown in table 2.

15. The isolated nucleic acid according to claim 13 or 14, wherein said nucleic acid comprises a mutation at codon 454 resulting in a replacement of alanine by threonine in said calcium channel.

16. The isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a deletion.

17. The isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a frameshift at codon 1266.

18. The isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a mutation which results in aberrant splicing.

19. The isolated nucleic acid according to claim 18, wherein said aberrant splicing is of intron 28.

20. An isolated nucleic acid encoding a calcium channel subunit or a functional fragment

thereof, wherein said nucleic acid is obtained from a mammal diagnosed as having one or both of familial hemiplegic migraine and episodic ataxia type 2.

21. The isolated nucleic acid according to claim 20, wherein said calcium channel subunit is a β2 subunit, wherein said nucleic acid is derived from, related to or associated with a gene which in humans is present on chromosome 10p12.

22. A method for identifying a gene which encodes a P/Q-type gated calcium channel, said method comprising:

contacting genetic material with a a nucleic acid molecule or a fragment of fragments thereof according to claim 1 or claim 20.

23. The method according to claim 22 wherein said gene is related to an episodic neurological disorder.

24. The method according to claim 22, wherein said gene is related to migraine.

25. The method according to claim 22, wherein said gene is related to one or more neurological disorder selected from the group consisting of FHM, EA-2, and autosomal dominant cerebellar ataxia.

26. A method of distinguishing between alleles of a gene which encodes a P/Q-type gated calcium channel, said method comprising:

contacting said gene with a nucleic acid molecule or a fragment of fragments thereof according to claim 20.

27. The method according to claim 23 or claim 26, wherein said gene is of human origin.

28. The method according to claim 23 or claim 26, wherein said gene is identified in a cell or an animal.

29. A recombinant expression vector comprising a nucleic acid molecule according to claim 1.

30. A cell or an animal comprising a vector according to claim 29.

31. A transgenic non-human cell, an isolated transgenic cell or a non-human transgenic animal comprising a nucleic acid molecule according to claim 1.

32. A non-human cell, an isolated cell or a non-human animal comprising a gene which encodes a P/Q-type gated calcium channel identified by the method according to claim 28.

33. A non-human cell, an isolated cell or a non-human animal comprising a genome in which a nucleic acid corresponding to said nucleic acid according to claim 1 has been modified.

34. A method for screening for an agent useful for treating FHM, EA-2, SCA6, migraine or other neurological disorder associated with cation channel dysfunction, said method comprising:

comparing phenotypic characteristics relating to cation channel dysfunction of a first animal contacted with said agent with those of a second animal not contacted with said agent, wherein the genome of said first animal and said second animal comprise a nucleic acid encoding dysfunctional $\alpha 1$ subunit of a P/Q-type gated calcium channel, whereby an agent useful for treating FHM, EA-2, SCA6, migraine or other neurological disorder is identified by a decrease in phenotypic characteristics relating to calcium channel dysfunction in said first transgenic mouse in comparison to said second transgenic mouse.

35. A protein or peptide comprising an amino acid sequence encoded by a nucleic acid

molecule according to claim 1.

36. A natural or synthetic antibody directed against a protein or peptide according to claim 35.

37. A method for diagnosing FHM, EA-2, SCA6, migraine or other neurological disorders associated with cation channel dysfunction, said method comprising:

detecting a protein or a peptide encoded by the nucleic acid according to claim 38 in a patient.

38. The nucleic acid according to Claim 1, wherein said nucleic acid comprises one or more mutation which results in dysfunction of said calcium channel.

39. A non-human animal with phenotypic characteristics relating to calcium channel dysfunction, the genome of which comprises:

a nucleic acid encoding dysfunctional $\alpha 1$ subunit of a P/Q-type gated calcium channel.

40. The non-human animal according to claim 39, wherein said non-human animal is a mouse.

Respectfully submitted,

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